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NEUROLOGICAL EMERGENCIES

Current management of ischaemic stroke

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Epidemiological studies have quantified the seriousness of stroke. Its incidence averages 179 per 100 000 per year worldwide with a prevalence of 500–600 per 100 000. Eight to 20% of its victims die in the first 30 days.[1] Early recurrence adds to the neurological deficit and lengthens hospital stay. Late recurrence affects 4%-14% per year and five year survival averages only 56% for men, 64% for women.[2] Overall, recurrence contributes to the $16 billion in health care costs and lost productivity seen annually in the USA alone.[3]

Once considered untreatable, ischaemic stroke has become subject to emerging therapies and is entering a new era, one that justifies an article focusing on treatment as well as the expected issues of diagnosis and delineation of risk factors. Increases in the understanding of the pathophysiology of stroke subtypes is steadily improving the outlook for more specific therapies for stroke analogous to the changes in outlook for myocardial infarction. Frustrated hopes for older therapies have given way to renewed confidence in newer lines of approach. Evidence from animal studies and preliminary clinical trials suggests that the ischaemic process may require several hours to develop, offering the possibility of preventing irreversible infarction. Uncontrolled intracellular influx of calcium is the current major culprit, though doubtless others will be as well documented in future. Antioxidants, free radical scavengers, and more exotic agents to block the developing necrosis after arterial occlusions are not yet well enough understood to predict their future in stroke therapy. Some of the older therapies such as anticoagulation are making a comeback whilst surgery for some indications has at last proved of value.

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Hyperacute therapy for ischaemic stroke

Thrombolytic therapy

Increasing experience with thrombolytic agents, mainly recombinant tissue plasminogen activator(rTPA), has demonstrated instances of significant and sustained neurological improvement when thrombolytic treatment is initiated within the first few hours. Better outcomes are generally associated with documented recanalisation of the artery feeding the symptomatic region. What remains uncertain is whether the timing of therapy is more important than specific dose and whether delays increase the risk of complications, negating any benefits.

A multicentre, Phase I trial evaluated the safety and efficacy of intravenous administration of rTPA in the treatment of acute ischaemic stroke.[4 5] Patients were stratified and evaluated separately for those treated within 90 minutes[4] and between 91 and 180[5] minutes of onset of stroke. An open-label, dose escalation study design was used. Ninety four consecutive patients were treated with intravenous rTPA at one of 7 doses, over 60 or 90 minutes. Subsequent use of anticoagulation was at the discretion of the investigators. Endpoints included intracerebral parenchymal haematoma (ICH), haemorrhagic transformation without ICH, systemic haemorrhagic complication, death, major neurological improvement at 2 and 24 hours, and neurological deterioration.

Of the 74 patients treated within 90 minutes, 32% had a decreased level of consciousness, 37% had gaze deviation, and 40% had hemiparesis. Major neurological improvement at 2 hours occurred in 30%, correlating with smaller infarct size, but not with patient age, race, gender, infarct location, severity of initial deficit, or presence of oedema. Improvement at 24 hours occurred in 46%. Neurological deterioration occurred in 11% (2 with ICH) at 24 hours, and in 8% at 7–10 days. Six patients had died at 30 days and 6 more by 3 months. Asymptomatic bleeding occurred in 4% and was not dose related. Symptomatic bleeding correlated only with total dose. The three patients (4%) who developed intracerebral haemorrhage (ICH) within 24 hours had all received doses greater than 0·85 mg/kg. Of the 20 patients treated at 91–180 minutes under the same study design, two had fatal ICH and three had major neurological improvement after 24 hours. Those who died had received higher doses (0·85 or 0·95 mg/kg).

Three other studies,[6-8] based on angiographic criteria for the diagnosis of arterial occlusion, utilised intravenous rTPA within 6 hours of onset of stroke. Recanalisation was demonstrated angiographically in 20–50%, asymptomatic haemorrhagic conversion in 30–40%, haemorrhage causing deterioration or death occurred in 10%, and good clinical outcome at 24 hours in 40%. Intra-arterial thrombolysis with urokinase or streptokinase has also demonstrated some beneficial results in retrospective analyses.[9 10]

These encouraging findings have so far been in open-label studies and leave unresolved how well they compare with the natural history. In a recent study assessing 29 strokes within 12 hours of onset, 24% showed spontaneous improvement within the first hour after baseline examination, and 52% had improved by 18 hours after onset of stroke.[11] Spontaneous recanalisation has been documented in individual cases by angiogram or by Doppler[12] in the same time frame as that from TPA, so eventually studies will have to involve a placebo group. At present, the main issues of safety are being studied in the hope that the justification for placebo studies will eventually be shown.

Neuronal rescue: calcium channel antagonists

In vitro studies and animal models have indicated a pathological role of calcium entry in neuronal injury.[13–18] Ischaemia induces the release of excitatory amino acid neurotransmitters such as glutamate and glycine which promote calcium entry into neurons via such receptor-mediated membrane channels as the kainate, the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and the N-methyl-D-aspartate (NMDA) channels. A variety of enzymatic reactions follow, including those mediated by calmodulin. Destruction of neurofilaments, disruption of cell membrane integrity and consequent cell death most likely result from the production of nitric oxide and the subsequent formation of other free radicals. The NMDA channel has at least 6 sites which may be susceptible to pharmacological blockade.[19] The glutamate recognition site has been blocked experimentally by the compound CGS-19755, the glycine site by HA-966, the "upper competitive site" by MK-801, NS-1102, and d-Methorphan, the polyamine site by Ifenprofil, and another competitive site by Mg++. At a sixth site—a site of phosphorylation—no antagonist has yet been identified. Enzymatic inhibition of nitric oxide synthetase by N-nitro-L-arginine also appears to protect against glutamate neurotoxicity.[17] Efficacy of these agents in humans awaits clinical trials.

Voltage-dependent calcium channel antagonists are the only agents which have reached the clinical trials stage. Verapamil, diltiazem and nifedipine have poor brain penetration and have never been considered viable candidates for cerebral protection. Nicardipine was evaluated in a small phase I trial. Thirty five patients were randomised to receive 3–7 mg/kg/hour IV infusion versus placebo.[20] All patients showed improvement, with a slight difference favouring nicardipine. No further studies were performed.

The greatest experience to date has been with nimodipine, which has less systemic effects than the other calcium channel blockers and penetrates the blood-brain barrier well. In a large multicentre trial of subarachnoid haemorrhage,[21] infarction was reduced by 34% and poor outcome by 40%. Early trials for ischaemic stroke using 120 mg/day showed decreased mortality when treatment was administered within 24 hours of stroke onset, but no significant difference in long-term functional recovery. The largest trial, conducted by the Nimodipine Study Group,[22] enrolled 1064 patients for 21 days in doses of 60 mg, 120 mg, or 240 mg per day compared with placebo. Heparin was allowed in cases of suspected cardioembolic stroke. Exclusion criteria included intracranial haemorrhage and significant co-morbidity. Although no significant differences in mortality or neurological function were seen across the groups for the overall cohort treated within 48 hours of stroke, subgroup analysis of those patients treated with 120 mg/day within 18 hours of stroke onset showed significantly better outcome scores and a 30% reduction in frequency of deterioration. Benefit also correlated with negative initial brain CT.

Although this trial only among nine double-blind, placebo- controlled studies showed such significant benefit, the numbers of those treated early in the other trials was too small for individual analysis. A meta-analysis of all nine trials, totalling 3714 patients, indicated a benefit for those receiving early therapy: the 616 patients treated within 12 hours showed a pooled odds ratio of 0·62 favouring nimodipine (95% CI, 0·44–0·87).[23] No effect on outcome was seen for age, sex, hypertension, diabetes, or cardiac disease. There was no drug effect for those treated 13–24 hours, and a slightly worse outcome for those treated after 24 hours. Further studies appear in order, but at the least, useful therapy seems in the offing. The human studies corroborate the animal models which emphasise the importance of early intervention.

Heparin

Unlike thrombolytic therapy, anticoagulation with IV heparin is not intended to dissolve thrombus, but to impair the thrombogenesis created by the "clotting cascade". Experience with warfarin and heparin dates back decades, and one might be forgiven for thinking that their usefulness has long been established; such is not the case. Brought early into clinical practice and never subjected to the kinds of trials demanded nowadays, warfarin anticoagulation has long been the standard treatment for patients with rheumatic mitral stenosis and prosthetic valves but is not likely to undergo any such trial in the near future. The debate on heparin use has continued unabated and only lately have major trials been mounted to establish its usefulness. Only two clinical trials in the CT era evaluated the effect of heparin anticoagulation in the treatment of acute stroke. One study treated patients with cardioembolic stroke and demonstrated probable benefit. The other study failed to show a treatment effect in non-cardioembolic stroke.

The first study[24] reported 45 patients randomised with presumed cardioembolic stroke to immediate anticoagulation with IV heparin versus delayed anticoagulation with warfarin after 14 days. The IV heparin group received a bolus of 5000–10 000 units of heparin within 48 hours of stroke onset, followed by a

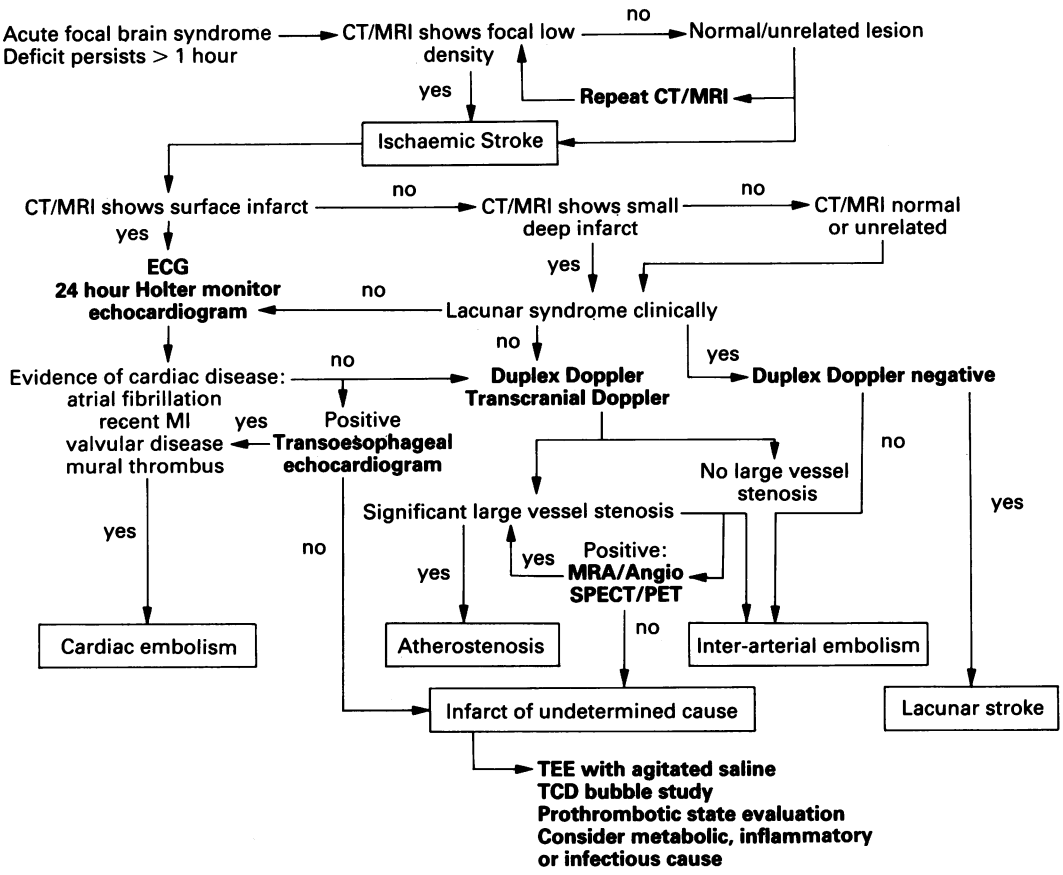

Figure Diagnostic algorithm for ischaemic stroke

Table Medical therapies for ischaemic stroke

Therapy	*Agent*	*Comment*
Protect brain metabolism		
Anaesthesia, hypothermia, barbiturates	various	No proven value
Nitric Oxide inhibitors	L-arginine	In Vitro studies[18]
Calcium channel antagonists		
Voltage dependent	Nicardipine	Slight benefit[20]
	Nimodipine	benefit <12h[22 23]
	PY 108-068	inconclusive[120]
Receptor dependent (NMDA receptor)	CGS-19755	In clinical trial[19]
	HA-966	In vitro studies[19]
	Mg++	In vitro studies[19]
	MK-801	Trials cancelled[19]
	NS-1102	In vitro studies[19]
	d-methorphan	In clinical trial[121]
	Ifenprofil	In vitro studies[19]
Lysis occluding clot		
thrombolytic agents	rTPA	Phase I trials[4 8]
	Urokinase	Anecdotal benefit[9]
	Streptokinase	Anecdotal benefit[10]
Suppress systemic response to brain ischaemia	Naloxone	No proven value
Reduce Sludging		
Haemodilution	LMWD	No proven value
Red cell deformation	Pentoxifylline	No proven value
Anti-oedema agents	Steroids	No proven value
	Hyperosmolar agents	No proven value
Vasodilators	Nitroglycerine	No proven value
	Prostacycline	No proven value
Anticoagulants		
Intravenous	Heparin (pork, beef)	Conflicting results[24 25]
	Heparinoids (ORG 10172)	In clinical trial[27]
Oral	Warfarin	In trial v Aspirin[122]
Platelet antiaggregants		
Cyclo-oxygenase pathway	Aspirin	In trial v Warfarin[122]
cAMP phosphodiesterase pathway	Dipyridamole	No benefit alone[123]
	Sulfinpyrazone	No benefit alone[34]
Combined	Ticlopidine	Benefit v ASA in some[47 50]

maintenance infusion to keep the partial thromboplastin time (PTT) at 1·5–2·5 times the patient's baseline. After at least 96 hours of heparin the study group was switched to long-term anticoagulation with warfarin. Patients younger than 18 or older than 78 were excluded, as were those with persistent severe hypertension. Of the 24 patients randomised to early anticoagulation there were no recurrences and no haemorrhages during the two week study period. Of the 21 patients randomised to receive delayed anticoagulation, two had early recurrent embolism, one had a deep vein thrombosis, two had haemorrhagic con-

versions and two died. The study was terminated early because of the strong trend toward benefit in the study group, despite the small sample size.

The second study[25] randomised 225 patients to receive either IV placebo or heparin within 48 hours of stroke onset, with a target PTT of 50–70 second. The study period was seven days and no long-term anticoagulation was given. Patients were excluded from the study if they had a possible cardioembolic source, if their deficit was too severe or resolved before the start of therapy, if previous deficits existed, or if stroke progression was noted within one hour of study onset. No significant differences in stroke progression or death was seen at seven days. No difference in functional level was seen at one year. There were significantly more deaths in the heparin group at one year, although most of these deaths occurred 3–12 months after the initial stroke and "appeared unrelated to treatment."

Both studies suffered from a small sample size. They established that early recurrence was not so common as to make estimation of any therapeutic effect an easy task. Because the first study focused on cardioembolic stroke and the second excluded such patients, the conflicting conclusions cannot be directly compared. A subsequent meta-analysis[26] was unable to show a benefit of anticoagulation, although most trials surveyed were before CT. The findings were of sufficient interest that a multicentre trial is underway in the USA to compare a synthetic heparin with placebo in acute stroke.[27] No studies have so far determined whether differences for stroke exist according to the route of administration (IV or subcutaneous) or if IV whether continuous or bolus, or the exact dose and duration of therapy. The matter is not trivial since evidence favouring similar effects for intermittent subcutaneous heparin could easily allow treatment at home. Similarly, if continuous IV administration is needed, it could be given by subcutaneous pump, in either case sparing hospital expense in ambulatory patients.

Prevention of recurrence or first stroke

Whereas the treatment of stroke in the hyperacute phase is under intense study, better established but no less controversial is the initiation of prophylaxis for those at high risk and the long term management of stroke in the hope of preventing recurrence.

Long term oral anticoagulation

Large epidemiological studies, for which the Framingham Study[28] is a model, have established a high risk for stroke in patients with cardiac disease. The highest risk was seen in patients with atrial fibrillation in combination with valvular disease. The overall risk of stroke in patients with chronic atrial fibrillation is 5% per year. With the decline in incidence of rheumatic heart disease and rising uncertainty of the best management for non-valvular atrial fibrillation, such patients have been considered suitable for such trials. Three large prospective, double-blind trials indicate a benefit for long term anticoagulation and a low risk of serious complications.[29–32]

The three studies were the Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation Study (AFASAK),[29] the Stroke Prevention in Atrial Fibrillation study (SPAF)[30 31] and the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF).[32] Overall, patients on warfarin had a 69% reduction in stroke risk in an "intention to treat" analysis and an 83% reduction in an "on-treatment" analysis.[33] Patients with strokes in the warfarin groups were no more likely to have haemorrhagic than ischaemic strokes. The rate of major bleeding was nearly identical for the warfarin and control groups at about two per cent; minor bleeding was three times more likely in the warfarin group.

The design of the studies varied slightly. All three studies excluded highest risk cardiac patients; those with recent embolic events, recent myocardial infarction and significant congestive heart failure or cardiomyopathy were not enrolled. SPAF excluded patients with lone atrial fibrillation, randomising them to aspirin or placebo groups only because of a low stroke risk of <0·5% per year. AFASAK excluded patients with paroxysmal atrial fibrillation for the same reason. The level of anticoagulation differed slightly. AFASAK used a prothrombin time of 1·5–2·0 times control, SPAF a prothrombin time of 1·3–1·8 times control, and BATAAF a prothrombin time of 1·2–1·5 times control. For the control groups AFASAK used ASA 75 mg/day or placebo, SPAF used 325 mg/day or placebo and BATAAF allowed ASA or no treatment to be used at the discretion of the investigators.

The AFASAK study randomised 1007 patients over a two year period. The unblinded warfarin group showed an incidence of transient ischaemic attack (TIA), stroke or systemic thromboembolism of 2% per year compared with a 5·5% incidence in the ASA and placebo arms. Three of the 5 strokes in the warfarin group had strokes when they were off warfarin. Non-fatal bleeding occurred in 6% of the warfarin group (43% of these were found to have inflammatory or malignant disease) compared with 1% in the control groups. A drawback to this study was that 38% of patients in the warfarin group dropped out, mostly because of the inconvenience of frequent blood samples.

The SPAF study randomised 1330 patients and was terminated early at a mean follow up period of 1·3 years. The incidence of stroke or systemic embolism was 2·3% in the warfarin group, 3·6% in the ASA group, and 7·4% in the placebo group. In this study as well, four of six patients with ischaemic stroke in the warfarin group had strokes off therapy. Major bleeding complications were comparable in the warfarin, ASA, and placebo groups at 1·5%, 1·4% and 1·6%, respectively.

Of the 420 patients randomised in the BAATAF study, followed for an average of 2·2 years, ischaemic stroke occurred in the warfarin group at a rate of 0·41% per year and in

the control group at 2·98% per year for a risk reduction of 86%. The two strokes in the warfarin group occurred at prothrombin times of <1·2. Among the strokes in the control group, eight of 13 occurred in patients taking aspirin. The death rate in the warfarin group was 2·25% and in the control group, 5·97%. Two fatal haemorrhages occurred, one presumed ICH in the warfarin group and a pulmonary haemorrhage in the control group. Minor bleeding occurred in 38 patients in the warfarin group and in 21 patients in the control group.

Antiplatelet therapy

Aspirin therapy in primary and secondary stroke prevention has been widely employed because of its ease of administration, documented prophylactic effect in coronary artery disease, and because physicians and the public perceive it as a benign treatment. This last point is not entirely to its advantage: many patients (and some physicians) continue to think of it as adjunct therapy and often fail to mention its use when questioned about medications being taken. Other antiplatelet drugs such as sulfinpyrazone and dipyridamole used alone have not proved beneficial in clinical testing.[34]

More than ten randomised placebo-controlled trials of aspirin following TIA or minor stroke have been completed.[35–45] Most showed a significant risk reduction with aspirin. Given the decline in stroke incidence over the past decades, modern clinical trials of stroke prevention require approximately 1000 patients to be enrolled and followed for an average of five years to detect a 50% difference at a significance level of $p < 0{\cdot}05$.[46] Smaller studies may suggest benefit when none exists or overlook a true benefit.

Of the four largest clinical trials—the UK trial,[35] the European,[36] the French,[37] and the Canadian[38]—all found some degree of benefit, ranging from 20% reduction in stroke and vascular death in the British trial to 50% reduction in stroke and stroke-death in the French trial. Two slightly smaller trials, the Danish[41] and the Swedish,[43] found no benefit. The Danish study used an ASA dose of 50–75 mg per day and the Swedish study entered only patients who had suffered major strokes. Differences from other studies are of uncertain significance. A lack of benefit in women, reported in the British and Canadian studies, may have been due to a lack of statistical power, as the risk of stroke and stroke recurrence is lower for women. The optimum dose of aspirin remains controversial. The Dutch trial for stroke prevention after TIA showed no difference between 30 mg/day and 283 mg/day.[45] The UK trial found no difference between 300 mg/day and 1300 mg/day but the meaning of the data have been disputed. The SPAF trial[31] in patients with atrial fibrillation found a benefit of ASA 325 mg/day, in a setting of atrial fibrillation, not TIA or prior stroke. Consequently, it remains unresolved whether ultra-low-dose aspirin or aspirin in doses as high as 1300 mg/day offer slight, wide, or no major differences in rates of first or recurrent stroke. The only source of agreement is that the higher doses produce more disagreeable gastrointestinal side effects.

Ticlopidine, a platelet antiaggregant newly available in North America, has been in use in Europe and the rest of the world for over 15 years. Its maximum antiplatelet action is at a dose of 500 mg/day, it reaches maximum effect at 3–5 days, and its effects last the lifetime of the platelets. Adverse side effects include gastrointestinal disturbance in 20% which may resolve with temporary dose reduction, rash in 10%, neutropenia in 2·4%, and severe neutropenia in 0·8% which is seen in the first few months and is reversible. Significant haemorrhage occurs in < 1% and gastrointestinal bleeding is 3 times less common in patients taking 500 mg of ticlopidine than 1300 mg of ASA.[47] Two large clinical trials found a benefit over ASA and placebo.[47–49]

The Canadian-American Ticlopidine Study (CATS)[49] randomised 1053 patients with recent non-cardioembolic stroke to receive ticlopidine 250 mg twice daily or placebo. The study excluded patients who had significant co-morbidity and those with TIA alone. The incidence of primary endpoints (ischaemic stroke, myocardial infarction, and vascular death) was 10·8% in the ticlopidine group versus 15·3% in the placebo group for a relative risk reduction of 30·2% by "on-treatment" analysis. Intention-to-treat analysis concluded a 23% risk reduction for the treatment group. Fifty two per cent of patients in the ticlopidine group and 40% of those in the placebo group discontinued treatment. Relative reduction in stroke or stroke death was found on secondary analysis to be 33·5%. Ticlopidine proved equally effective in men and women.

The Ticlopidine-Aspirin Stroke Study (TASS)[47] randomised 3069 patients to ticlopidine 250 mg twice daily or ASA 650 mg twice daily. They included patients with TIA, transient monocular blindness, or minor stroke. Average follow up period was 2·3 years. In their intention-to-treat analysis, they showed a 12% reduction of stroke or death. In a three year follow up, the incidence of fatal or non-fatal stroke was reduced 21%. Twenty one per cent of the ticlopidine group and 14·5% of the ASA group discontinued the medicine.

For those who tolerate the medicine, ticlopidine appears to have a slight advantage over aspirin and a definite advantage over placebo in secondary stroke prevention. In a subsequent subgroup analysis of the two studies,[50] the patients who appeared to benefit more from ticlopidine than aspirin included women and those for whom aspirin therapy had failed. Patients with diabetes mellitus requiring treatment, those on antihypertensives, and those with elevated creatinine levels also showed greater treatment effects versus aspirin. It remains to be determined whether the slight improvement in stroke event rates, compared with aspirin, will offset the side effects and difficulties in monitoring to allow ticlopidine to become popular.

Modification of risk factors

A striking decline in age-specific stroke morbidity and mortality has been noted over the last 15 years in both women and men, with mortality rates falling in industrialised countries by 4·1%-7·1%.[51 52] Modification of diet and smoking behaviour, a decline in rheumatic heart disease, and improved treatment of hypertension and coronary artery disease have contributed.[51] Factors that influence stroke incidence include age greater than 65 and male gender.[53] Blacks are twice as prone to stroke as whites and Hispanics,[54] even when controlling for a higher incidence of hypertension.[3] The difference for blacks has persisted throughout the period of overall declining mortality rates. Crucial to the management of stroke is an understanding of epidemiological predictors of stroke and stroke recurrence. Modification of risk factors has been shown to produce dramatic reductions in stroke risk.[55]

Among modifiable risk factors, hypertension overshadows the rest. From the Framingham Study, hypertension confers a relative risk of 4·0 for men and 4·4 for women. Borderline hypertension confers a relative risk of 2·0 and even isolated systolic hypertension, previously thought to be benign, carries a relative risk of 2·4.[1] One overview of 14 randomised drug trials showed a 40% reduction in stroke risk in patients able to lower their diastolic blood pressures an average of 6 mm Hg.[56]

The risk of smoking appears to be dose related: light smokers are twice as likely as the general population to develop stroke, heavy smokers (> 25 cigarettes per day) four times as likely. Five years after cessation of smoking, the risk approaches that of the general population.[57 58] Diabetes mellitus confers a relative risk of 1·5 to 3·0, probably secondary to microvascular disease and a greater tendency to atherosclerosis.

Cardiac disease is a complex risk factor. Atrial fibrillation in the setting of rheumatic valvular disease confers a 17-fold risk and a 5-fold risk exists for non- valvular atrial fibrillation.[28] A relative risk of 2·0 is seen for those with coronary artery disease, recent myocardial infarction, and congestive heart failure.[59 60] Left ventricular hypertrophy in the setting of advancing age and hypertension confers a relative risk of 4·0.[1] Increased risk may also be seen in patients with patent foramen ovale, mitral valve prolapse, atrial septal aneurysm, and aortic arch disease.[61]

A variety of laboratory abnormalities have been shown to correlate with higher stroke incidence. Elevated[62] and decreased[63] haematocrit may contribute, as well as protein C and S deficiencies, elevated fibrinogen,[3] and lupus anticoagulant/anti-cardiolipin antibodies[64–66] and antithrombin III levels.[6 7] Most studies find a relationship between elevated lipids and atherosclerosis in both coronary and carotid artery disease.[1 3]

Mild to moderate alcohol intake appears to confer a protective effect for ischaemic stroke with a relative risk of 0·3–0·5, whereas heavy drinking increases stroke risk, particularly for haemorrhagic types.[68–70] Alcohol may be more associated with stroke recurrence.

Transient ischaemic attack may be considered both a manifestation and a risk factor for stroke. As a risk factor, TIA confers an independent relative risk of 3·9.[71] TIA precedes stroke in 10% to 14% of cases.

Because the rate of stroke recurrence is so high—ranging from 4% to 14% per year depending on the study—factors have been sought which independently influence stroke recurrence. In the Lehigh Valley study, the relative risk for recurrence was 41·4 for TIA, 8·0 for MI or other coronary artery disease, 5·6 for diabetes mellitus, and 4·5 for hypertension. Unlike initial stroke risk, age and sex did not influence recurrence.[53] The Stroke Data Bank found that hypertension, glucose level, and stroke subtype predicted 30 day recurrence, and only hypertension predicted a two year recurrence.[72] The 30 day recurrence rate of stroke varied from 2·2% for lacunar syndromes to 7·9% for large artery atherosclerotic disease to up to 14% in the first two weeks for atrial fibrillation. A recent small case-control study identified potential cardioembolic aetiology as the single significant factor for 90 day recurrence.[73] Cardiac disease and hypertension lower survival for recurrent stroke.[72]

In evaluating an individual patient's risk for stroke, the entire risk factor profile should be considered. Multiple risk factors are cumulative as in the case of hypertension which confers a relative risk of 4·0: adding coronary artery disease increases the relative risk to 8·4.[1]

Surgical intervention

Carotid endarterectomy was introduced in 1954.[74] At that time, even though its efficacy had not been proved, the operation grew in popularity from 15 000 in 1971 to 105 000 in 1985.[75] Following the 1985 trial that suggested extracranial-intracranial bypass procedure (EC-IC) to be an ineffective therapy,[76] a series of randomised clinical trials were initiated to assess the efficacy of endarterectomy. Three large, multicentre trials addressed the question of operating in the setting of symptomatic carotid artery disease.[77–79] Results from these trials demonstrate a 10–18% relative reduction in stroke risk for endarterectomy in high grade (>70%) stenosis. Mild to moderate disease as well as the question of asymptomatic carotid stenosis remain under investigation.

The North American Symptomatic Carotid Endarterectomy Trial (NASCET)[77] drew data from 50 centres in the USA and Canada, randomising patients to surgery and the best medical therapy (mostly ASA 1300 mg/day) or medical therapy alone. The patients were stratified to 30–69% stenosis or 70–99% stenosis documented by angiogram. After 659 patients had been randomised in the high-grade stenosis group—half the number projected to be needed to prove a 10% risk reduction—the study was terminated because of a dramatic therapeutic benefit favouring surgery. The cumulative risk of ipsilateral stroke at two years was found to be 9% in the surgical group and 26% in the medical group for a risk reduction of 17%. The cumulative risk of major or fatal ipsilateral stroke was 2·5%

in the surgical and 13·1% in the medical group. The risk of all strokes was 12·6% versus 27·6%, and the risk of death or major stroke was 8% versus 18·1% for the surgical and medical group respectively. Average perioperative morbidity and mortality for all centres involved was 5·8%. Perioperative incidence of major stroke or death was 2·1%. The 30–69% stenosis group is still under investigation.

Another multicentre trial, the Veterans Administration study,[78] randomised 189 patients with greater than 50% internal carotid artery (ICA) stenosis to surgical plus medical therapy (ASA 325 mg) versus medical therapy alone and found similar results. At a mean follow up of 11·9 months, crescendo TIAs and stroke were found in 7·7% of patients in the surgical group versus 19·4% in the medical group for a risk reduction of 11·7%. Patients with greater than 70% stenosis showed a risk reduction of 17·7%. Perioperative morbidity and mortality in this study was 5·5%.

The largest, longest running trial is the European Carotid Surgery Trial (ECST)[79] which also found a striking benefit of surgical intervention for high grade carotid stenosis among the 2518 patients they recruited. Their comparison groups were surgery plus aspirin versus aspirin alone. The high-grade stenosis (>70%) portion was terminated for this trial as well after a 9·3% risk reduction was noted for stroke or death in less than 30 days and a 9·6% reduction in stroke or death at three years. Recruitment continues in this study also for patients with 30–69% stenosis.

What to do with asymptomatic carotid artery disease is less certain. Bruits are present in some 4–5% of the general population age 45 to 80. The reported risk of carotid stenosis without symptoms varies widely in the literature. Oft-quoted is a relatively small study which followed 50 patients with >50% stenosis and found stroke in 4·5% and TIAs in 16·5%.[80] At the other extreme is a study following asymptomatic stenotic carotid arteries contralateral to operated symptomatic arteries which found no strokes in a 20 year follow up period.[81] Non-uniformity of definitions and follow up contributes to the problem in defining risk. In the Asymptomatic Carotid Artery Stenosis Study (ACAS),[82] a large multicentre trial currently addressing the issue, 20% of patients have positive CT scans in the distribution of the "asymptomatic" ICA. Further, evidence of prior strokes may be found in up to 17% of all stroke patients presenting with their "first" acute stroke.[83]

Supplementary laboratory data may help assess the significance of a carotid stenosis. Positive emission tomography may identify areas of "misery perfusion" in the borderzone regions representing tissue at risk that could be better perfused after operation. Regional cerebral blood flow (rCBF) measurements may show low flow areas as well as areas of decreased vasoreactivity following CO_2 inhalation. The existence of adequate collaterals may be inferred by the re-establishment of low resistance flow in the CCA on duplex Doppler (ECA to ophthalmic to ICA collateral) or a reversal of flow in the anterior cerebral artery (ACA) on transcranial doppler (collateral via the anterior communicating artery).

The one published multicentre trial of asymptomatic carotid stenosis (CASANOVA)[84] randomised 410 patients to surgery and medical therapy (ASA 330 mg, dipyridamole 75 mg) versus surgery alone. Those with >90% stenosis were excluded. Their end points were stroke or death. Patients were removed from the study and operated on if a TIA occurred in the ipsilateral territory, if >90% stenosis developed, or if there was bilateral disease >50%. There was no difference between the two groups, however, the exclusion of patients with more severe arterial disease and the study's small size leaves the issue unresolved. The ACAS trial may produce more data on the risk of asymptomatic disease at all degrees of stenosis.

Recommendations for management

From the outset of the encounter with an acute stroke patient, the conscientious clinician must accrue sufficient data to make informed and timely management decisions. Settling the diagnosis of stroke subtype is no longer a mere academic exercise but can help predict likely outcome and direct therapy. From the history, TIAs, hypertension, increased blood glucose concentration, cardiac disease, and stroke subtype predict recurrence. Particular attention should be paid to indicators of cardioembolic source such as recent MI, arrhythmias or congestive heart failure. Headache suggests subarachnoid bleeding in the absence of focal signs. When severe headache coincides with focal signs, lobar haemorrhage is more common than ischaemic stroke.[85] Pain in the neck, side of face, teeth or jaw, or retro-orbital area may indicate vertebral or carotid artery dissection, even without a history of neck trauma.

The physical examination can give an impression of the size and a fair estimate of the location of the infarct, and thus guide the urgency of subsequent management steps. Hemiparesis and forced gaze deviation suggests a large hemisphere or critical brainstem lesion, particularly if accompanied by decreased level of consciousness, whereas hemiparesis involving the face, arm and leg in an alert patient suggests a small, deep lesion involving a confluence of motor fibres. When isolated, behavioural abnormalities such as aphasia or hemineglect without a gaze preference suggest smaller hemisphere lesions. General examination may reveal a carotid bruit, and physical examination and an electrocardiogram an arrhythmia, or signs of cardiomyopathy or congestive heart failure.

MRI should identify all but the smallest lesions and is superior to CT for brainstem and small, deep, so-called lacunar infarcts. CT is equal to MRI in documenting an infarct within the first hours[86] and is better for a diagnosis of acute haemorrhage or bony abnormalities. Either technology may miss an infarct within the first couple of hours of onset.

Data collected should suggest stroke aetiol-

ogy. Fifteen to 30% of strokes are embolic from a cardiac source such as atrial fibrillation or valvular disease. Although 5–6% of patients may have a fluctuating course, the classic clinical presentation of cardioembolic stroke is of sudden deficit, maximal at onset.[87 88] Syndromes more likely to be embolic include hemianopia without hemiparesis, pure Wernicke aphasia, and ideomotor apraxia.[89] CT and MRI which show a single cortical branch territory infarct also are consistent with an embolic source because atheroma rarely extends to the surface vessels, although the source of the inferred embolus may not be readily apparent even after full evaluation. Mainstem branch occlusions are also often embolic, but local atherostenosis is a possibility in such a setting as well. One difficult pitfall on initial CT is the deep-lying lucency involving the internal capsule and basal ganglia of some 2 to 3 cm in size, apparently sparing cortex, which can be labelled as a large lacune. Often such instances are also of embolic origin, involving several lenticulostriate branches of the middle cerebral artery from temporary occlusion of the middle cerebral stem, followed by rapid collateralisation from anterior or posterior cerebral branches or recanalisation of the occlusion with distal migration of the embolus. A right-to-left shunt, usually a patent cardiac foramen ovale, can be inferred when transcranial Doppler shows microbubbles in the intracranial vessels after injection of 10cc of agitated saline in the antecubital vein[90] and contrast transoesophageal or standard transthoracic echocardiography usually can find the defect in the cardiac atrial wall or mitral valve prolapse.[61] Holter monitoring may infer a cardiac emboligenic source by documenting atrial fibrillation.

In 15% of cases, severe large vessel atherosclerosis is present and seems responsible for the stroke. It is best appreciated when there is severe extracranial internal carotid stenosis or occlusion and the "distal field" lesion is imaged on CT or MRI as an infarct high over the convexity, spreading caudally from the borderzone between arterial territories.[91 92]

The most common clinical profile of this type of infarct is fractional arm weakness (shoulder different from hand). Male gender, hypertension, and diabetes mellitus appear significantly more common in this group than in patients with cardioembolic stroke.[93] Although the standard angiogram most reliably demonstrates large vessel stenosis, when it is severe enough to be of haemodynamic significance, duplex Doppler usually readily delineates the severity of the internal carotid stenosis and shows high velocity, turbulent flow. Intracranial internal carotid artery stenosis may produce detectable high resistance flow on Doppler examinations of the extracranial carotid. Transcranial doppler often shows dampened pulsatility in the ipsilateral middle cerebral artery.[94–99] Duplex Doppler in combination with magnetic resonance angiography is rapidly becoming a reliable alternative to the more invasive traditional angiogram. Cerebral blood flow measurements with Xenon CT, SPECT, and rCBF techniques are also being used to evaluate regional hypoperfusion.

In perhaps 15% of all stroke, large vessel atherosclerosis with less than haemodynamic stenosis (<80% occluded or with an ulcerated plaque) occurs in the absence of a cardioembolic source and the cause is attributed to an artery to artery embolus. Embolic fragments may arise from atherosclerotic lesions in the ICA,[100–102] the basilar artery,[103] intracranial large vessels,[104 105] the proximal stump of an occluded carotid,[106] or the distal tail of a thrombus in an occluded ICA. Distinguishing inter-arterial embolism from possible cardioembolic aetiology may be difficult, however, the former usually produces a smaller cortical infarct and the latter is more often associated with a decreased level of consciousness and an abnormal initial CT.[93]

Small deep lesions in the subcortical white matter, the thalamus, the basal ganglia or the pons accompanied by an appropriate clinical syndrome suggest lacunar disease, accounting for 15–20% of all stroke.[107–109] Arteriolar wall lipohyalinosis, microatheroma, or even microemboli may produce the pathology.[110] Early studies described only a handful of classic syndromes, but case reports have expanded the number to greater than 70.[111] Positive scans in the capsule, adjacent corona radiata, thalamus or pons have been reported for clumsy hand-dysarthria, ataxic hemiparesis and hemiballism; pure sensory syndromes have been associated with small thalamic lesions.[112] CT scanning is positive in only half of lacunar strokes,[112 113] with MRI increasing the yield.[114] Larger lacunes are more often symptomatic. Hypertension is the risk factor most associated with lacunar infarction.

Despite efforts to arrive at a diagnosis, the cause of infarction in up to 40% of cases remains undetermined. This may result from an inability to perform appropriate laboratory studies because of the patient's advanced age or co-morbidity, or because of unwillingness on the part of the physician or patient. It may also result from improper timing of tests, such as an angiogram performed after an embolus has cleared, or a CT or MRI done before the infarction appears. In a majority of these cases, however, appropriate testing done at the proper time produces normal or ambiguous findings. Evaluation of patients classified as "Infarct of Undetermined Cause" in the Stroke Data Bank revealed certain common features.[115] They tended not to have had previous TIAs, infarcts, carotid bruits or cardiac risk factors. Fifty seven per cent had clinically relevant CT images; surface infarcts were found in 40%. Hemispheral syndromes predominated in 66% and basilar syndromes occurred in 15%. Twenty seven per cent worsened in the hospital and 41% had moderate to severe weakness. Some of these cases may be explained by hypercoagulable states from protein C, free protein S, fibrinogen, lupus anticoagulant or anti-cardiolipin antibody abnormalities.[116–118] Others may have had paradoxical emboli through a patent fora-

men ovale.[61 119] Migraine, meningitis, dissection, arteritis, or inherited metabolic abnormality may explain rare cases. Rather than force a classification into one of the four established categories, we recommend maintaining the classification of infarct of undetermined cause until a definite cause can be established.

Conclusions

Pending the resolution of management issues by on-going clinical trials, those who have read this far are offered our current recommendations to use heparin to prevent recurrence and limb thrombophlebitis in cases of suspected small or moderate-sized cardioembolic stroke. While signs of minor haemorrhagic infarction on brain imaging are no bar to such therapy, it is still wise to withhold heparin in any case where the diagnosis could include systemic or parenchymatous intracranial haemorrhage. Large and disabling strokes are often complicated by haemorrhagic transformation even without anticoagulant therapy, and the dim outlook for a functional recovery further constrains plans for anticoagulation. If anticoagulation is to be considered long term, brain re-imaging in 48–72 hours before initiating anticoagulation is worthwhile to exclude haemorrhagic conversion.

Suspected artery-to-artery embolism demands prompt investigation to see if the source can be found and removed surgically. Prophylactic endarterectomy is indicated for haemodynamically-significant symptomatic carotid atherosclerosis unless the acute stroke is severe, and it is our practice to use IV heparin until the exact degree of stenosis is determined by doppler, MRA, or angiogram.

Long term, there have so far been no scientifically-established bases for management decisions for warfarin or antiplatelet therapy. Based on the superiority of aspirin or warfarin over placebo in prevention of first stroke in a setting of atrial fibrillation, it is inferred, but not yet established, that some therapy after the first or subsequent stroke is preferable to none. A 30 centre American trial is to soon start comparing aspirin with warfarin in the prevention of recurrent stroke. Pending the outcome of such trials, antiplatelet therapy or anticoagulation are options for patients at risk for recurrent stroke. For those with less than 70% large artery stenosis, the NASCET continues to randomise patients. Those not participating should be followed with doppler monitoring at intervals of three, six to 12 months to document those who progress to more than 70%, who would then qualify for surgery. For syndromes of lacunar stroke, antiplatelet agents remain popular but anticoagulants might also be beneficial, the latter to be avoided in those with poorly-controlled hypertension. Ticlopidine may be used if it is tolerated, and should be considered particularly if the patient is a woman or if aspirin therapy has failed. Careful attention to the neutrophil count is essential. The utility of other therapies for acute stroke, including thrombolytic therapy and neuronal rescue by calcium entry antagonists, await the outcome of continuing clinical trials.

No data exist as to the ideal duration of chronic prophylactic therapy. Provided reliable and regular monitoring is maintained, patients with atrial fibrillation should probably be followed indefinitely on warfarin, keeping the prothrombin time 1·2 to 1·5 times control. The duration and type of therapy for prevention of recurrence in any other setting of stroke have no firm basis but evidence suggests therapy is more beneficial than simple neglect.

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